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# Pediatric Formulation Development: Challenges and Opportunities from an Industry Perspective

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Subcommittee of the Oncologic Drugs Advisory Committee**

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# Goal

- **“The joint goal for industry, regulators, practitioners and patients is to encourage paediatric drug development in order to create a situation where substantially more children have access to safe and effective medication...”**

From European Federation of Pharmaceutical Industries and Associations (Efpi)  
2009 position paper “Industry Perspectives on Pharmaceutical Development of  
Medicines for Paediatric Use”



# Requirements for pediatric formulations

- **Age-appropriate formulations**
  - Appropriate route of administration
  - Appropriate dosing volumes (oral and injectable)
  - Appropriate excipients and levels
  - For oral formulations – Palatable
  - Appropriate stability and taste acceptance
- **Ease of dosing and patient compliance**
  - Dosage form child can take / caregiver can administer
- **Dose flexibility while maintaining accuracy and safety**
- **Patient accessibility**



# What are Industry's considerations?

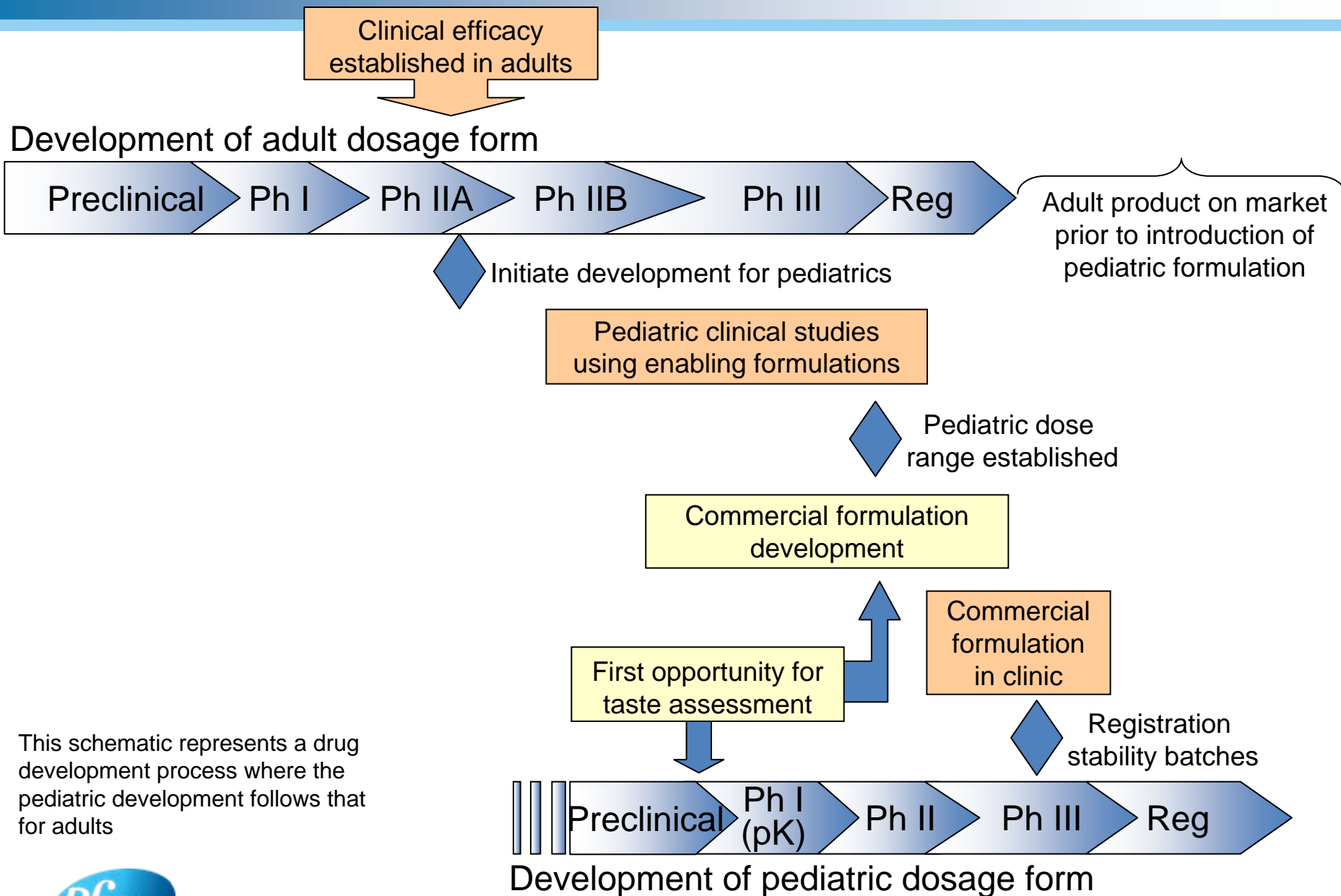
- **Generally aim to develop products for Global markets, but do need to consider market preferences and needs**
  - For example, is potable water freely available if required?
- **Meet the needs of the patient - maintain flexibility in dosage form design that meets patients' needs and fulfils regulatory requirements**
  - Scientific, risk-based approach on a case-by-case basis that ensures adequate quality, safety, and efficacy
- **Protect intellectual property rights**
- **Use of “enabling” formulations**
  - Enabling formulations are preliminary, simple formulations
    - Example: Powder Active Pharmaceutical Ingredient (API) in a bottle
  - Facilitate clinical study timelines while assuring product quality and patient safety
  - Development of commercial product can be progressed in parallel



# Challenges in developing pediatric formulations

- **Diversity of children**
  - Size/weight increases >20-fold from birth to adulthood
  - Dose adjustments of >4-fold often needed
  - Ability to take medicines and dosage form preferences vary greatly with age
- **Taste masking**
  - Taste acceptance can impact patient compliance
    - Taste perception/preferences are different in children than adults, disease state can also impact taste/smell perception
- **Stability – chemical, physical, microbial**
  - Oral liquids present additional stability challenges due to additional excipients needed for palatability
    - Typically are aqueous based formulations, therefore increasing the importance of microbial control measures
  - Expiration period may be too short to support commercial feasibility
- **Achieving global regulatory acceptability**
- **Providing rapid patient access**
- **Accelerated development timelines**





This schematic represents a drug development process where the pediatric development follows that for adults



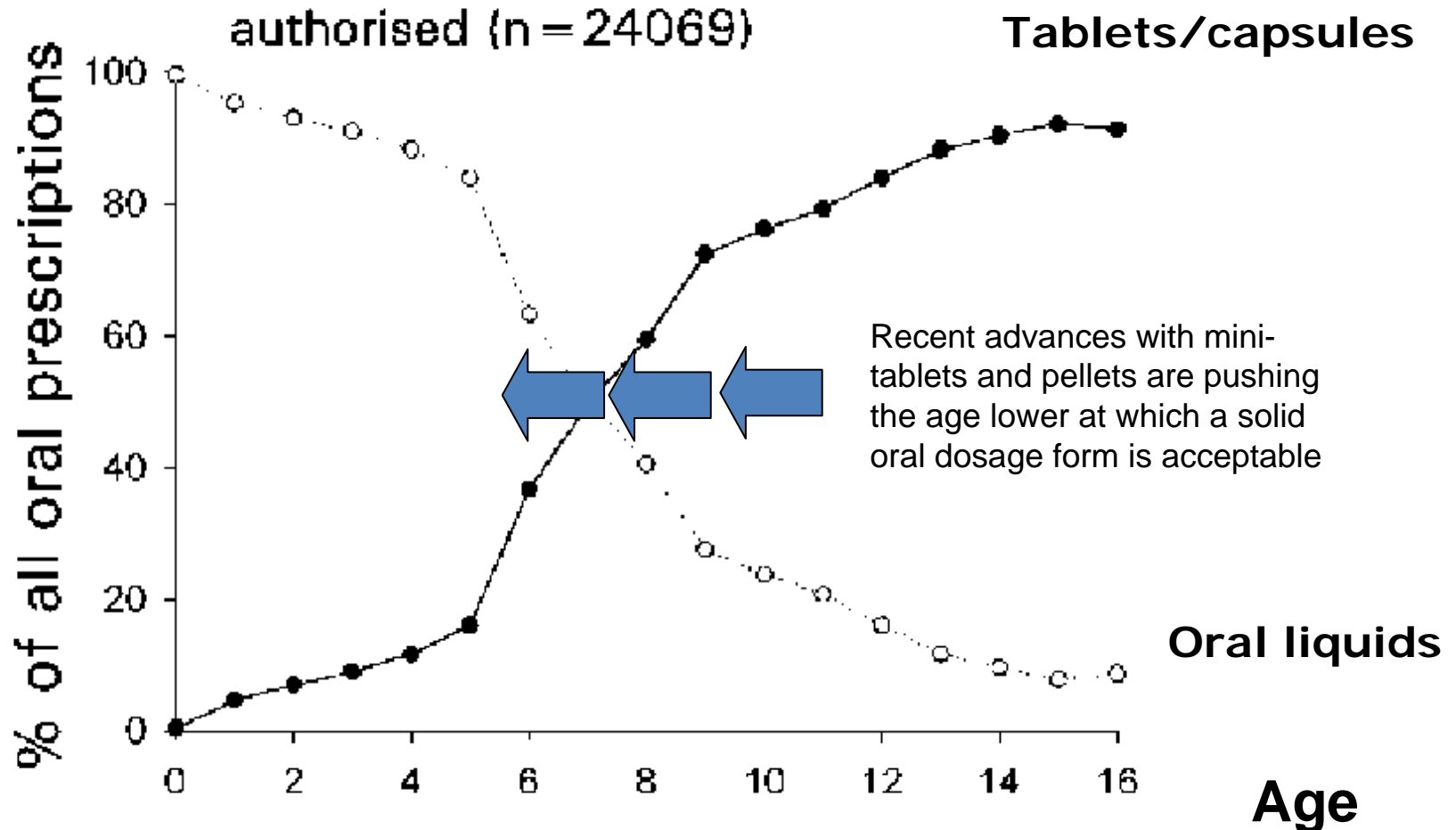
# Pediatric marketed formulations

- **Oral (50%+ currently marketed)**
  - Liquids (suspensions, solutions, syrups, concentrates)
  - Granules, sprinkles, powders
  - Fast-dispersing dosage forms (films, fast-melts, ODTs)
  - Tablets (mini-tablets, chewable tablets)
- **Injectable**
  - Primary consideration is delivery of desired dose in appropriate volume for pediatric patient
  - May require reformulation of adult product
- **Others**
  - Suppositories, topical creams/ointments, eye/ear/nose preparations, inhalation products

**From Schirm E et al. *Lack of appropriate formulations of medicines for children in the community*. Acta Paed 2003; 92: 1486-9**



# At what age can children take tablets?



# Excipients – why they are needed?

- **The goal is to only include excipients at levels that are required to deliver the dosage form to the patient**
  - **To improve solubility**
    - Solvents, co-solvents, surfactants
  - **To ensure physical, chemical and microbial stability**
    - Buffers, anti-oxidants, suspending agents, preservatives
  - **To improve palatability and patient compliance**
    - Flavours, sweeteners, taste modifiers, sensate materials
  - **To control release**
    - Polymers, coatings
  - **To improve manufacturability**
    - Glidants, bulking agents



# Oral liquids can be challenging



- **Palatability is critical to compliance**
  - Many different methods to assess palatability
    - Adults vs. children
    - Trained expert panelists vs. volunteers vs. patients
    - In vitro methods – “e-tongue”
  - Early work on palatability is needed to keep the development timelines on track, but you need to know the target doses!
  - Compounds are not selected based on “taste”, many of our drugs are extremely bitter
- **Solubility and physical/chemical/microbial stability considerations**
  - Compatibility with excipients may present additional stability challenges
  - Preservatives typically needed for multi-use products

# Case History: Developing a “simple” liquid formulation for pediatric use

- **Drug X is currently marketed as granules in a capsule for adults**
- **FDA requested a dosage form suitable for children starting at age 2 years**
  - Dose flexibility is a key requirement
- **To support the clinical program, an enabling formulation was developed**
  - Open and sprinkle commercial capsule contents on apple sauce or yogurt
- **Challenges to developing an oral liquid formulation for this product**
  - Active Pharmaceutical Ingredient (API) is not stable in solution
  - API is strongly coloured and staining
  - Taste is unknown, but anecdotal information suggests a metallic taste
- **Approaches in progress for commercial formulation**
  - Development ongoing using existing granules, looking at multiple dosage form options such as film-coated mini-tabs or film-coated granules that can be dose titrated and sprinkled on food
  - Due to instability in solution and metallic taste, oral liquid has low probability of success
- **Impact on overall project**
  - The complexity of the stability challenges and the potential taste issue will extend the development timeline
  - There is still a lot of work to do, and we may end up needing to develop several distinct products to support dose flexibility across the pediatric population



## Case History: Developing an injectable for pediatric use

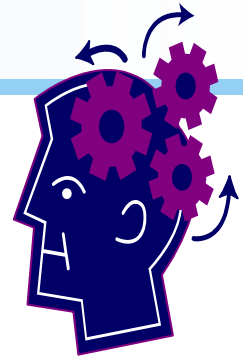
- **Drug Y currently marketed as lyophile for reconstitution and dilution prior to dosing in a Hospital setting**
  - Adult product is single-use vials
- **To support clinical program, the adult product was used with modified dosing administration instructions to cover the pediatric studies**
- **Pediatric dose flexibility is critical, while minimizing the potential for accidental overdosing**
- **For pediatric use, in certain cases a pediatric specific presentation may be needed based on a risk-based option assessment**
  - If the risk is high for Hospitals to use the same vial for multiple patients/doses (current product is single use without preservatives)
  - If the risk is high for dosing errors (each pediatric vial would contain a lower total dose in a differentiated packaging)
- **This risk-based approach maintains flexibility and focuses efforts on what adds the most value to the patients**



## “Extemporaneous Preparation” or “Compounding”

- **When is it useful?**
  - When there is not a suitable product available for pediatric use
  - As enabling formulations to facilitate clinical studies
  - When additional dose titration is needed
  - When there is a shortage of commercial pediatric formulation
    - Recent example with Tamiflu oral suspension shortage
- **Potential Risks**
  - There may be a lack of information and data on product compatibility and stability in the compounded state
  - Any manipulation of a product has the potential to introduce dosing errors or change the bioavailability of the drug
  - Exposure of health care worker or caregiver during the compounding steps
- **How can Industry reduce risk?**
  - “Industry-verified” formulation and preparation methods provides supportive stability and dose verification data
  - Recent example - [Emergency Compounding of an Oral Suspension from TAMIFLU Capsules \(Final Concentration 15 mg/mL\)](#)





# Learnings

- **Plan early – pediatric strategy must be an integral part of the development plan**
- **Formulation development can be very challenging**
  - Apply good scientific principles
  - Consider overall risk / benefit
  - Seek flexibility and compromise
- **Discussion helpful to ensure proposed formulations meet regulatory expectations**
  - The patient is waiting
  - “Preferred” dosage form may not be achievable

# Hopes for the future

- **Continue to increase our knowledge base**
  - Dosage form acceptability
  - Excipient safety
  - Chemical structure vs. taste predictability
- **Achieve more rapid, cost-effective development of suitable (global) formulations using platform technologies**
- **Continued collaboration between regulators, industry, academia and practitioners towards a mutual goal**



## For more information...

Formulation of medicines for children; Tony Nunn & Julie Williams; Br J Clin Pharmacol (2005) 59:6 674–676

Paediatric and geriatric drug delivery; Jörg Breitzkreutz & Joachim Boos; Expert Opin. Drug Deliv. (2007) 4(1):37-45

Challenges of developing palatable oral paediatric formulations; Anne Cram, Jörg Breitzkreutz, Sabine Desset-Brethes, Tony Nunn, Catherine Tuleu, On behalf of the European Paediatric Formulation Initiative (EuPFI); International Journal of Pharmaceutics 365 (2009) 1–3

Pharmacokinetics in the Child; Crom, William R; Environmental Health Perspectives Volume 102 (1994), Number S11

Lack of appropriate formulations of medicines for children in the community; Schirm E et al; Acta Paed (2003); 92: 1486-9



# Thank You!

**Thanks for the opportunity to present an  
Industry perspective on the challenges  
and opportunities related to the  
development of pediatric appropriate  
formulations**

